REMARKS

Claims 28 and 29 are pending in the application. Claims 1-27 and 30-40 have been withdrawn. Claims 41-43 are new.

Drawings

As the Examiner will note, the title appearing on Fig. 8i has been amended to correctly identify the oligonucleotide tested as REP 2021. Support for such amendment is found in paragraph [00114]. This error was only noticed upon preparation of the present response. Additionally, it was noticed that Applicants never received a draftperson's notice of acceptance of the drawings. The drawings currently on file are substitute drawings for those originally filed. However, at the time of substituting the drawings, the sheet containing Figs. 8a-8c was omitted. Accordingly, the omitted sheet is submitted herewith. Since Figs. 8a-8c were filed originally with the application, the introduction of this new sheet containing these figures does not constitute new subject matter.

Claim objections

Claim 28 has been objected to because it is dependent on non-elected or withdrawn claims 1-4. As requested by the Examiner, claim 28 has been re-written in independent form. In addition, claims 41-43 have been added to protect the subject matter of claim 28 when dependent on claims 2-4.

Claim rejections - 35 U.S.C. § 112

Claim 28 has been rejected under 35 U.S.C. § 112, second paragraph. The Examiner states that claim 28, being dependent on claim 4 which contains the language "does not consist essentially of...", fails to define the sequence of the oligonucleotide in the claimed invention. In order to overcome this rejection, Applicants point out that new claim 43 now encompasses an antiviral oligonucleotide of at least 6 nucleotides in length and the sequence of said oligonucleotide is not complementary to an mRNA of said target virus and is free of polyA, polyG, Gquartet or a TG-rich sequence. New claims 42 and 43 have been added in order to claim the subject matter of claim 28 when dependent on withdrawn claims 3 and 4.

Support can be found in paragraph [0063] of the description. Thus, the expression "does not consist essentially of..." is no longer found in claim 28 or new claims 42 and 43. In view of the arguments and amendments presented hereinabove, reconsideration of the Examiner's rejection is respectfully requested.

Claims 28 and 29 have been rejected under 35 U.S.C. § 112, first paragraph. The Examiner states that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner further states that claim 28 being dependent on claim 3 reads on the said oligonucleotide as "40 nucleotide in length", as previously elected, but the specification does not clearly specify which sequences of 40 nucleotides are used for the instant invention. In order to overcome this rejection, Applicants respectfully point out that the description discloses the use of the oligonucleotides REP 2006 (40mer randomer; page 93), REP 2021 (40mer sequence; Paragraph 114 and Fig. 8I), REP 2018 (40mer sequence; Paragraph 114 and Fig. 8F), REP 2024 (40mer randomer; Paragraph 171 and Fig. 11A), REP 2029 (40mer polyA sequence; Paragraph 359-360 and Fig. 37), REP 2031 (40mer polyC sequence; Paragraph 359-360 and Fig. 37), REP 2030 (40mer polyT sequence; Paragraph 359-360 and Fig. 37), REP 2055 (40mer polyAC sequence; Paragraph 359-360 and Fig. 37), REP 2056 (40mer polyTC sequence; Paragraph 359-360 and Fig. 37) and REP 2057 (40mer polyAC sequence; Paragraph 359-360 and Fig. 37). In addition, Figures 4, 7, 10 and 18c all disclose results demonstrating the antiviral activity of oligonucleotides of 40 nucleotides in length. Thus, the present application discloses randomers, random oligonucleotides and specific sequences of 40 nucleotides in length with no specific structural features others then those claimed in claims 28, 29, 41-43. For example, a person skilled in the art when considering the structural characteristics of REP 2006, will acknowledge that such oligonucleotide, by the way it is prepared as per the specification, contains at most one possibility for every possible sequence for a 40 nucleotides in length oligonucleotide. Consequently, claims 28, 29, 41 and 42 have been amended to specifically encompass an antiviral oligonucleotide containing at least one phosphorothioate linkage wherein the antiviral activity of said oligonucleotide occurs principally by a sequence independent mode of action. Support can be found on pages 13 and 15 of the description. Page 13 of the description, and more specifically paragraph

[0057], has been amended to clarify the intended definition of a non-sequence complementary mode of action. One skilled in the art would acknowledge that a non-sequence complementary mode of action inherently means that the anti-viral activity occurs principally by a sequence-independent mode of action. The amendment made to paragraph [0057] does not introduce any new subject matter. Thus, the claims now on file encompass the common structural features of the oligonucleotides encompassed by the present application. In addition, Applicants respectfully point out to the Examiner that claim 28 is no longer dependent on claim 3. In view of the arguments presented hereinabove, reconsideration and withdrawal of Examiner's rejection are earnestly solicited.

Claims 28 and 29 have been rejected under 35 U.S.C. § 112, first paragraph. The Examiner states that the language of the claims is not strictly limited to *in vitro* treatments and encompasses prophylaxis or treating infected patients and as such does not have support in the specification. The Examiner further states that there is insufficient disclosure to reasonably predict that the methods and compositions of the instant specification would inhibit replication of a viral infection *in vivo*. This is merely an unsubstantiated assertion with no evidence to support the contention that *in vitro* studies of the specification are indicative of *in vivo* activity. The Examiner also states that there are no specific teachings in the disclosure that would allow one to have a reasonable expectation of success in transferring the *in vitro* method to treat infected patients. In order to overcome this rejection, Applicants respectfully point out that the USPTO is not entitled to substitute itself for the FDA in order to evaluate the clinical relevance of the present invention. In addition, it is believed that the present invention has clinical relevance and that the *in vitro* results disclosed in the present application do not diverge from *in vivo* responses. To support this latter allegation, enclosed is a Declaration of Dr. Jean-Marc Juteau, one of the inventors, reporting *in vivo* results obtained with eight (8) different *in vivo* models of viral infections (Simian Immunodeficiency Virus model, Friend Leukemia Virus model, Influenza virus model, respiratory syncytial virus, Herpes virus-2 model, Cytomegalovirus model, Ebola virus model and Vaccinia virus model). These *in vivo* models are often the only models available unless Applicants initiate Clinical phase III trials. From the results reported in this Declaration, it is clear that the teaching contained in the present application is predicative of success for *in vivo*

therapy. In view of the foregoing, reconsideration and withdrawal of the Examiner's rejection of claims 28 and 29 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Claim rejections - 35 U.S.C. § 102

Claims 28 and 29 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Andreola *et al.* The Examiner alleges that the document of Andreola *et al.* teaches a plurality of non-complementary anti-HIV random oligonucleotides that bind to the HIV component, RNase H. Two of the oligonucleotides are 81 nucleotides long and have an IC_{50} of 30 nM for HIV infectivity in cell culture. Applicants argue that, contrary to the present invention, Andreola *et al.* teaches the identification of oligonucleotides having an antiviral activity due to their sequence. Further, Andreola *et al.* discloses a screening of a library of oligonucleotides corresponding to 4^{35} possible sequences using the SELEX procedures. By this technique, they identified oligonucleotides having high affinity to RNAse H domain of HIV-1 RT. As described on page 10090 (first column, last paragraph) in Andreola *et al.*, some selected oligodeoxynucleotides are inhibitors of RNAse H activity while other are not. In consequence, the oligodeoxynucleotides need to have high affinity to RNAse H domain of HIV-1 RT to inhibit RNAse H activity. This demonstrates that Andreola *et al.* targeted specific sequences and that the activity is sequence dependent. Moreover, it is reported on page 10091 (first column, first paragraph), that the use of electrophoretic mobility retardation analysis of the interaction between selected DNA ligands and HIV-1 RT as appropriate to the fact that HIV-1 room temperature activity can be removed from an active selected oligodeoxynucleotide by substituting residues. This again demonstrates that the activity is sequence dependent. Finally, in cellular antiviral assays, Fig. 7 in Andreola *et al.* shows that two selected oligodeoxynucleotide are active while two others are inactive, demonstrating the sequence dependent antiviral activity. Andreola et al. never recognized that any sequence independent oligonucleotide having at least one phophorothioate linkage had antiviral activity. On the contrary, claims 28, 29, 41-43 claim oligonucleotides having an antiviral activity wherein said activity occurs principally by a sequence independent mode of action. Consequently, the claims now on file clearly encompass that antiviral activity occurs principally by a sequence independent mode of action. Support can be found on page 13 of

the description. No new matter is being hereby introduced. In view of the arguments submitted hereinabove, reconsideration of the Examiner's rejections is respectfully requested.

Claims 28 and 29 have been rejected under 35 U.S.C. § 102(e) as being anticipated by Peyman *et al.* (US Patent No. 6,013,639). The Examiner states that Peyman *et al.* teaches oligonucleotides where the nucleotides sequence is 40 nucleotides in length and the end of the oligonucleotides sequence is other than guanine. The oligonucleotides further have phosphorothioate bridges that increase cell uptake. In addition, Peyman teaches methods for the preparation of modified oligonucleotides with phosphorothioate bridges and that these oligonucleotides can be linked to molecules which have a favorable influence on the properties of antisense oligonucleotides. In order to overcome this rejection, Applicants respectfully point out that, contrary to the teaching of the present application, Peyman *et al.* teaches that the efficacy of the tested oligonucleotides is dependent on the presence of a 10 guanines extension at each extremity of the oligonucleotides. It is clearly stated in Peyman *et al.* (column 1 and 2, under the Summary section), that:

> *"It has now been found that a very simple option exists for significantly improving unmodified or modified oligonucleotides with regards to their nuclease resistance and cell penetration, so that their activity is substantially improved, by extending the oligonucleotides at the 3' end and/or 5' end by from one to 10 guanines.*
>
> *Surprisingly, the novel oligonucleotide also exhibit a tendency to associate or aggregate. It is possible that they too form G quartet structures by the association of two or more oligonucleotide. Such structures would protect against exonuclease degradation and lead to an increased uptake in cell."*(emphasis added)

These oligonucleotides adopt a « G quartet » structure, which is not required in the present invention. The present application neither claims nor teaches that the efficacy of the oligonucleotides claimed is dependent on the presence of a 10 guanines extension at each extremity of the oligonucleotides. On the contrary, there is no such constraint in the sequence of the oligonucleotides claimed in the presence invention. Furthermore, Peyman *et al.* never recognized that sequence independent oligonucleotides (with at least one

phosphorothioate linkage) had antiviral activity. In Peyman *et al.*, the modified oligonucleotides need to be directed to a specific target to exhibit activity. The specification of Peyman *et al.* is full of examples of antisense oligonucleotides that are directed to specific targets. See column 6, lines 11-12 and 30-31, column 7, lines 25-28, column 8, lines 29-30, column 10, lines 35-36, column 11, lines 4-5 and column 14, lines 14-15, among others. In fact, Peyman *et al.* only provides for the teaching of modified oligonucleotides for improving nuclease resistance and cell penetration. Peyman *et al.* suggests that the modified oligonucleotides have activity, such as antiviral activity, only if such oligonucleotides target specific viral targets through an antisense mechanism - with a sequence dependent mode of action. Again, nowhere does Peyman *et al.* recognize that sequence independent oligonucleotides with at least one phosphorothioate linkage had antiviral activity. In view of the arguments submitted hereinabove, reconsideration of the Examiner's rejections is respectfully requested.

Double Patenting

Claims 28 and 29 have been provisionally rejected on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 1-2 of co-pending Application No 10/661,099. In order to overcome this rejection, Applicants respectfully request the Examiner to hold the requirement for submission of a terminal disclaimer in abeyance until such time as either application is found to be in otherwise allowable condition.

Claims 28 and 29 have been provisionally rejected on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 1-38 of co-pending Application No 10/661,088. In order to overcome this rejection, Applicants respectfully request the Examiner to hold the requirement for submission of a terminal disclaimer in abeyance until such time as either application is found to be in otherwise allowable condition.

Claims 28 and 29 have been provisionally rejected on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 1-2 and 14-32 of co-pending Application No 10/661,097 and claims 1-38 of co-pending Application No 10/661,415. In order to overcome this rejection, Applicants respectfully request the

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Examiner to hold the requirement for submission of a terminal disclaimer in abeyance until such time as either application is found to be in otherwise allowable condition.

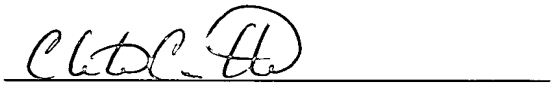
It is submitted, therefore, that the claims are in condition for allowance. Reconsideration of the Examiner's rejections is respectfully requested. Allowance of claims 28, 29, 41, 42 and 43 at an early date is solicited.

No additional fees are believed to be necessitated by this amendment. Should this be in error, authorization is hereby given to charge Deposit Account No. 19-5113 for any underpayment or to credit any overpayment.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully,

Date: August 11, 2006

By: 

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Enc. Drawing pages 8a-8c and 8g-8i
Marked-up Drawing page 8g-8i
Declaration of Jean-Marc Juteau

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AMENDMENTS TO THE DRAWINGS

Please replace the sheet of drawings containing Figs. 8g to 8i presently on file with the corresponding sheet of the drawings submitted herewith.

Please introduce a new sheet of drawings containing Figs. 8a to 8c submitted herewith.

Attachment: Replacement sheets of Drawings containing Figs. 8a-8c and 8g-8i; and
Replacement sheet of Drawings containing Figs. 8g-8i indicating the correction in red.

"Annotated Marked-up Drawing"

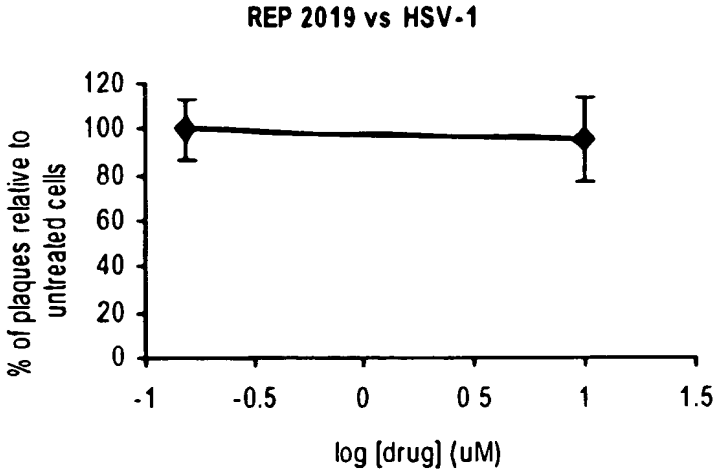

FIG. 8g

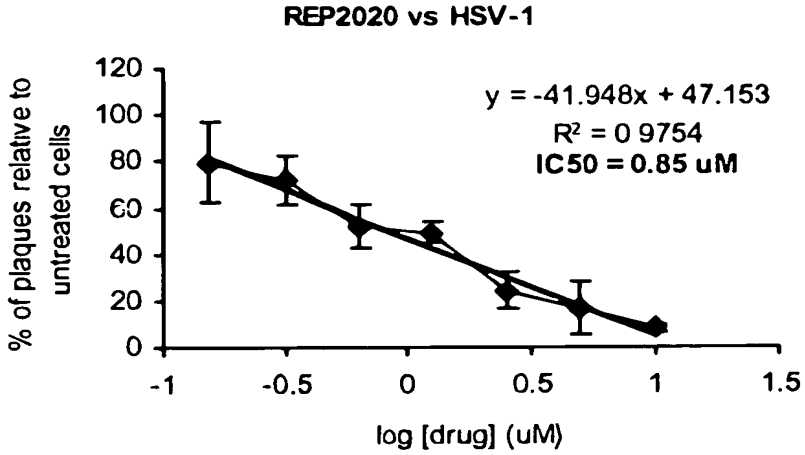

FIG. 8h

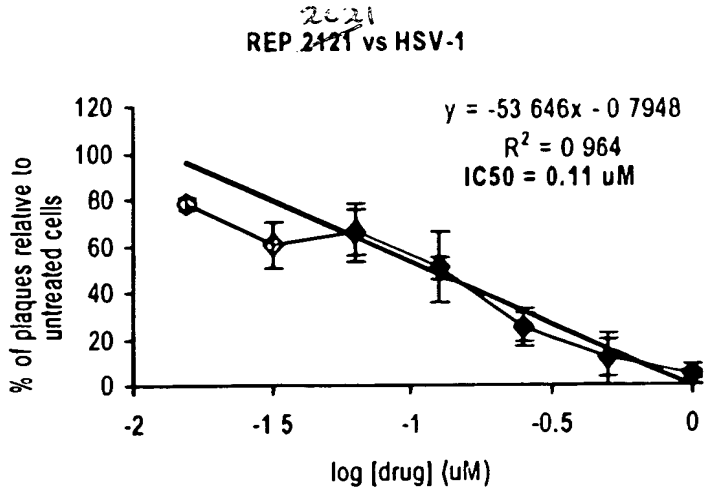

FIG. 8i